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Use of icodextrin in high transport ultrafiltration failure

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The presence or development of ultrafiltration failure (UFF) in patients on peritoneal dialysis (PD) has been the subject of increasing interest in the renal literature and the understanding of its causes and therapies continues to evolve [1–7]. An important aspect of these new insights is the greater clarity in definition and the recognition that clinical failure in maintaining volume homeostasis needs to be separated from true failure of ultrafiltration at the level of the peritoneal membrane [1–7]. This is particularly important because the refinement in the techniques of peritoneal dialysis, the greater reliance on automation, and the introduction of new osmotic agents have led to resolution of conditions that would have previously been labeled as ultrafiltration failure. The proper incidence of ultrafiltration failure, however, is at present difficult to determine because of the variability in case definition. If one considers failure of the peritoneal response to a 3.86%/4.25% glucose solution as an operational definition, then the incidence is rather low, especially during the first years of PD. However, if failure to achieve volume homeostasis is the criterion used, then a larger number of patients may be at risk of being labeled as having UFF. With the increasing tendency to tailor PD modality selection (CAPD vs. APD) to individual patient characteristics, and wide utilization of icodextrin, it is likely that older prevalence data will become irrelevant to guide current clinical practice.

The term loss of ultrafiltration capacity (UFC) has been used as a more precise term to help distinguish the clinical syndrome of fluid overload from a pathophysiologic alteration in the peritoneal membrane [2]. Such a precision is a felicitous development, and it is hoped that greater appreciation of the need for precise definition will allow the use of the term ultrafiltration failure to be limited to conditions associated with loss of ultrafiltration capacity. It is in this sense that the term ultrafiltration failure is used in the present article.

Table 1 offers a classification of ultrafiltration failure by pathophysiologic mechanisms. This classification will serve as a framework for the discussion of the role of icodextrin in helping correct the resultant clinical consequences.

Key words: renal replacement therapy, dialysate, volume homeostasis, CAPD, APD, peritoneal dialysis.

UF FAILURE DURING TRANSIENT HIGH TRANSPORT: PERITONITIS

Clinical and transport changes

Loss of UFC is a common clinical observation during episodes of peritonitis. Patients frequently exhibit negative net ultrafiltration with fluid retention and weight gain. Use of very hypertonic glucose solutions is common in the early stages of peritonitis, and adjustments in prescriptions are usually required until the inflammatory process has completely abated. Evaluations of transport parameters during episodes of clinical peritonitis have revealed several changes in transport characteristics that are summarized in Table 2 and illustrated in Figures 1, 2, and 3.

Detailed clinical evaluation of transport changes have been carried out in a limited number of studies [8, 9]. This is partly explained by the logistic hurdles of physiologic evaluations in acutely ill patients. Nevertheless, the available data provide a clear delineation of the transport changes, and these findings have been corroborated by observations in experimental animals. Only a few recent representative studies will be reviewed herein.

Douma et al recently described the transport consequences of peritonitis in fifteen patients undergoing continuous ambulatory peritoneal dialysis (CAPD) with 16 peritonitis episodes [9]. Patients were evaluated during the acute phase of the infection and after recovery by standard peritoneal permeability analyses [10]. The mass transfer area coefficients (MTACs) of low-molecular-weight solutes increased during peritonitis: urea 26%, creatinine 45%, and urate 45%. The MTAC of CO2, calculated to estimate peritoneal blood flow, was 71 mL/min (34 to 254 mL/min) during peritonitis and 55 mL/min (42 to 63 mL/min) after recovery, reflecting an increase in peritoneal perfusion. The peritoneal protein clearances were also greater during peritonitis, but this increase was

Table 1. Pathophysiologic classification of peritoneal causes of ultrafiltration failure

Mechanism	Condition
Rapid dissipation of glucose osmotic gradient	Fast transport status
Defects in fluid pathways	Impaired aquaporin function
Exaggerated contrary mechanisms	Lymphatic/tissue reabsorption
Loss of functional peritoneum	Adhesions

Table 2. Transport changes during peritonitis

Parameter	Change in MTAC	References
CO_2	↑	[9]
Urea	↑	[8, 9, 11]
Creatinine	↑	[8, 9, 11]
Urate	↑	[9]
Glucose	↑	[8, 9, 11]

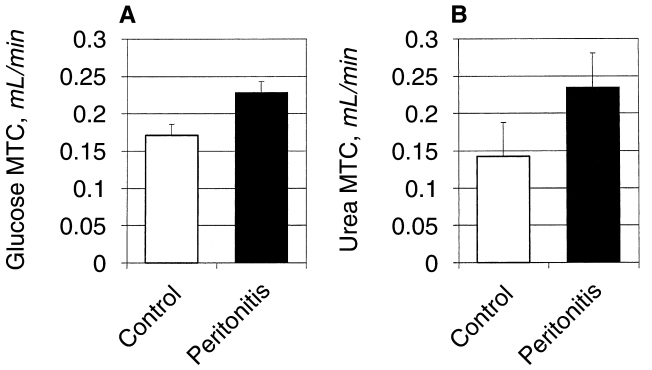

Fig. 1. In rats with lipopolysaccharide (LPS)-induced peritonitis, a significant increase was found in the diffusive transport measures for small solutes. Data are from reference [11].

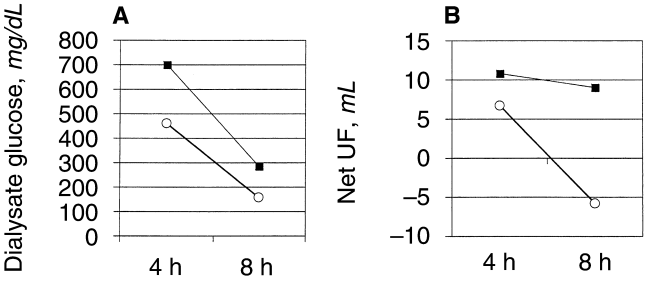

Fig. 2. Peritonitis results in a sharp decline in dialysate glucose and a parallel decline in net ultrafiltration, both changes being progressive with time. In long dwells (8 hours) the net ultrafiltration in rats with peritonitis becomes negative. Symbols are: (■) control; (○) peritonitis. Data are from reference [32].

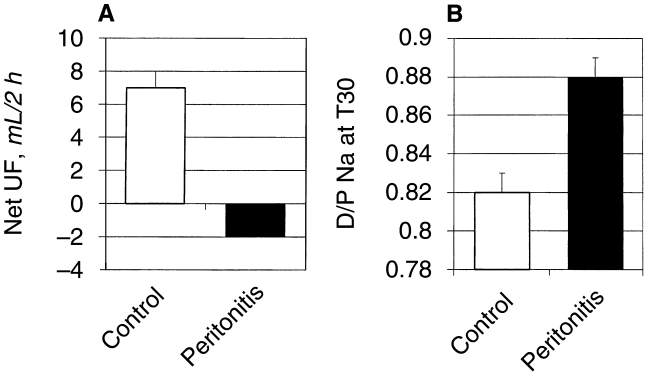

Fig. 3. The sharp decline in net ultrafiltration during peritonitis leads to the obliteration of the decline in dialysate sodium that is usually the result of water ultrafiltration via aquaporins. This is not due to any decline in the expression of aquaporins, but rather to their function or to increased sodium diffusion. Data are from reference [14].

not related to the molecular weight of the protein. The net ultrafiltration in all peritonitis episodes was lower as compared with the control dwells [9].

These clinical observations have been duplicated by several experimental studies. Wang et al recently examined the transport changes in an experimental model of peritonitis induced in rats by the intraperitoneal injection of lipopolysaccharide (LPS) [11]. The small solute diffusive transport rates were, in general, increased during peritonitis as compared with control (Fig. 1). The dialysate osmolality decreased much faster in the LPS treated group as compared with control, resulting in significantly lower transcapillary ultrafiltration. In LPS injected animals, net ultrafiltration was significantly lower (by 44%) as compared with the control group [11].

It is clear from clinical and experimental evidence that the loss of ultrafiltration capacity during peritonitis is due predominantly to the rapid dissipation of the glucose-dependent osmotic gradient. The observation that inflammatory conditions are associated with enhanced lymphatic absorption has led to the lingering misconception that this mechanism may be operative in peritonitis as well. This has been disproved by several studies [11, 12] including the recent work of Carlsson and Rippe [13]. They found that zymosan-induced peritonitis in experimental animals led to a marked increase in mass transfer area coefficients for small solutes (Fig. 4). This was paralleled by an increase of plasma-to-dialysate protein clearance (a measure of protein leak), and a decline in peritoneal-to-plasma labeled protein clearance (a measure of lymphatic absorption). Despite marked effects on peritoneal solute transport and on ultrafiltration, conceivably resulting from vasodilatation and increases in capillary permeability, zymosan-induced peritonitis did not cause any acute increases in the plasma appearance rate of IP instilled labeled albumin.

Taken together, clinical and experimental observations identify the ultrafiltration failure of peritonitis as a state of acute, transient, very high transport induced by the inflammatory process.

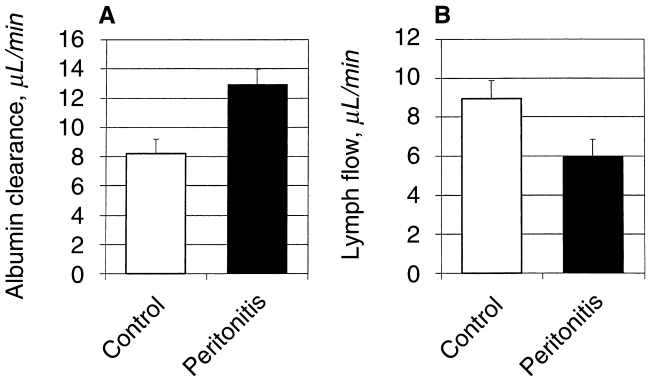

Fig. 4. Peritonitis results in increased leakage of proteins into the peritoneal cavity. Despite the presence of an inflammatory process, peritoneal lymphatic flow is not increased during peritonitis. Data are from reference [13].

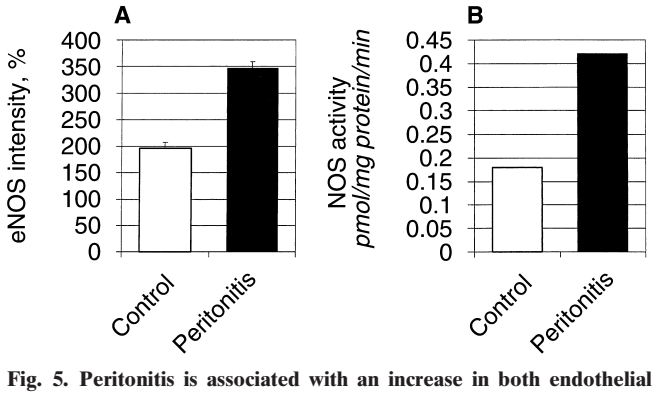

Fig. 5. Peritonitis is associated with an increase in both endothelial nitric oxide synthase (eNOS) expression in tissues and NOS activity. Data are from reference [14].

Table 3. Changes in selected mediators and mediator enzymes during peritonitis

Parameter	Change	References
NO synthase (inducible)	↑	[14]
NO synthase (non-inducible)	↑	[14]
PGE_2	↑	[9, 16, 17]
6-keto-PGF1 α	↑	[9, 16, 17]
Thromboxane B_2	↑	[9, 16]
Interleukin-1	↑	[23, 32]
Interleukin-6	↑	[16, 23]
Interleukin-8	↑	[17, 20]
Interleukin-10	↑	[32]
Transforming growth factor-beta	↑	[23]
Fibroblast growth factor	↑	[23]
TNF-α	↑	[21, 32]
INF-γ	↑	[32]
Hyaluronan	↑	[26–29]

Pathophysiology

Various inflammatory and vascular mediators are released into the peritoneal cavity during peritonitis. However, those involved in governing changes in peritoneal permeability to small solutes and protein remain incompletely defined (Table 3).

Experimental observations suggest that changes in nitric oxide (NO)-mediated vascular tone and permeability might be involved in the loss of UF during peritonitis [14]. In a model of acute peritonitis in rats, Combet et al observed that compared with controls, rats with peritonitis had a higher removal of plasma urea, a faster glucose absorption, high protein loss and a loss of UF [14]. Acute peritonitis in rats induced a major increase in total NO synthase (NOS) activity, which was inversely correlated with free-water permeability. The increased NOS activity was mediated by both inducible (Ca^{2+}-independent) and endothelial (Ca^{2+}-dependent) NOS isoforms (Fig. 5). In contrast, aquaporin-1 expression was unchanged in rats with peritonitis, but impaired aquaporin function was suggested by high dialysate/plasma ratios of sodium. These data suggest that a local production of NO, mediated by different NOS isoforms, might play a role in the transport changes occurring in peritonitis.

This is further strengthened by studies examining the effect of inhibition of NO synthesis on peritoneal transport during peritonitis. Breborowicz et al assessed the effect of an inhibitor of nitric oxide synthesis, N^G-nitro-L-arginine methyl ester (L-NAME), on peritoneal transport during peritonitis induced by intraperitoneal LPS in rats [15]. In the presence of L-NAME, LPS did not induce the expected changes in *trans*peritoneal transport of small and large solutes and did not cause a significant decline in net UF. L-NAME given intraperitoneally reduced both local and systemic production of nitric oxide, which might explain its effects on peritoneal transport. The increased expression of NOS during peritonitis and the prevention of the transport changes with the NOS inhibitor L-NAME suggest that nitric oxide is an important mediator of changes in peritoneal transport during peritonitis.

Validation of the above formulation by measurements of peritoneal effluent nitrate or nitrite (as measures of local NO production) has been difficult in both clinical [9] and experimental studies [16]. Studies of the peritoneal effluent of patients with peritonitis did not uncover any evidence of early changes in NO synthesis [9]. In 15 patients with peritonitis, Douma et al found no evidence for local production of nitrite or nitrate [9]. However, the MTAC of cyclic guanosine monophosphate (cGMP) was elevated 48 to 72 hours after the onset of peritonitis, which suggests the synthesis of NO. These clinical observations were interpreted to imply that the role of NO in mediating the changes during peritonitis is delayed [9]. Peritoneal effluent studies, however, may be insensitive to localized changes in NO synthesis uncovered in tissue expression experiments. Increased NO synthesis indeed may be responsible for the increased functional vascular surface area caused by peritoneal inflammation.

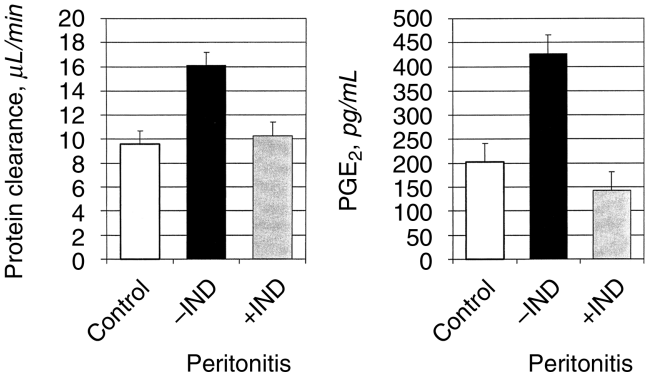

Fig. 6. Peritonitis is associated with increases in peritoneal protein clearance and intraperitoneal secretion of prostaglandin E_2 (PGE_2). Both of these changes are corrected by the intraperitoneal administration of indomethacin (IND) in the rabbit. Data are from reference [17].

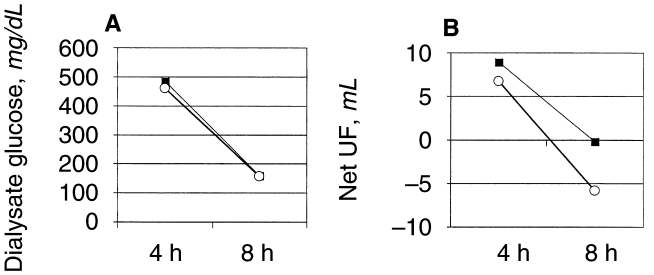

Fig. 7. Addition of hyaluronan (HA) to dialysis solutions during peritonitis has no effect on the dissipation of the glucose gradient, but still results in some attenuation of the degree of negative net ultrafiltration. Symbols are (■) peritonitis + HA; (○) peritonitis. Data are from reference [32].

The alterations in peritoneal permeability characteristics during peritonitis can be explained in part also by the increased concentrations of prostaglandins and cytokines in the dialysate [9]. In the acute phase of peritonitis the vasodilating prostaglandins E_2 (PGE_2) and 6-keto-$PGF_{1\alpha}$ were increased tenfold, while the increase in the vasoconstrictor thromboxane 2 (TxB_2) was only fivefold [16]. Using multiple regression analysis, the change in dialysate PGE_2 was related to the change in the intrinsic peritoneal permeability to macromolecules. No relationship was found between the increase in prostaglandin concentrations and the transport of β2-microglobulin, reflecting the effective peritoneal surface area. The above findings were reconfirmed during standardized four-hour dialysis exchanges [9]. The clinical observations were duplicated by Peng et al in an *E. coli* induced peritonitis model in the rabbit [17]. Inhibition of prostanoid production by intraperitoneal administration of indomethacin resulted in lower dialysate concentrations of the vasodilating prostaglandins both in patients [18] and in rats [17]. In the latter study an effect on peritoneal permeability to protein was found (Fig. 6), but this was absent in the study in humans [18]. Indomethacin in non-peritonitis patients inhibited 6-keto-$PGF_{1\alpha}$, but had no effects on peritoneal transport [19]. It follows from the above findings that prostaglandins are mainly involved in large pore peritoneal transport during peritonitis, but have no effect on the effective peritoneal surface area, which determines the transport of low molecular weight solutes like glucose.

Bacterial peritonitis leads to the release of proinflammatory cytokines from resident and infiltrating cells in the peritoneal cavity, which may have effects on transport (Table 2). Various studies have shown marked increases in dialysate concentrations of the proinflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor-α (TNFα) and IL-6, the chemokines IL-8, monocyte chemoattractant peptide-1 (MCP-1) and human melanoma growth stimulating activity (huGROα), and the growth factors transforming growth factor-β (TGF-β) and fibroblast growth factor (FGF) [16, 20–23]. The dialysate concentrations of IL-8 [20] and of huGRO [22] were related to the maximum number of neutrophils in effluent. Also, TGF-β complementary DNA (cDNA) molecules per macrophage were significantly greater than those of macrophages in non-infected peritoneal effluent. Relationships were found between the increase in the effective peritoneal surface area and that of dialysate IL-6 and TNFα [16]. These observations suggest an active release of proinflammatory cytokines and sclerogenic growth factors during peritonitis. It is unknown whether these factors might affect the physiological properties of the peritoneal membrane after recovery from the infection.

Hyaluronan (HA) is a polysaccharide that forms a critical component of extracellular matrices. HA is present in high concentrations in tissues undergoing remodeling and morphogenesis, and it appears to have an important role in the early stages of wound healing. Effluent hyaluronan concentrations in non-infected CAPD patients are higher than those in serum [24–29], suggesting local production, probably by mesothelial cells [28]. Patients with a large effective vascular surface area appeared to have higher effluent concentrations of hyaluronan than those with low D/P creatinine ratios [29]. Peritonitis causes a marked increase in dialysate hyaluronan [26–29]. This effect might be mediated by IL-1β [28]. Addition of exogenous hyaluronan to dialysis solutions causes higher ultrafiltration rates in rats, both in non-infected animals [30] and during peritonitis [31, 32], without any changes in the dissipation of the osmotic gradient (Fig. 7).

It is clear from the studies reviewed in the previous section that the functional changes observed during peritonitis are due to a combination of factors that act either synergistically or antagonistically to modify and modulate peritoneal transport (Fig. 8).

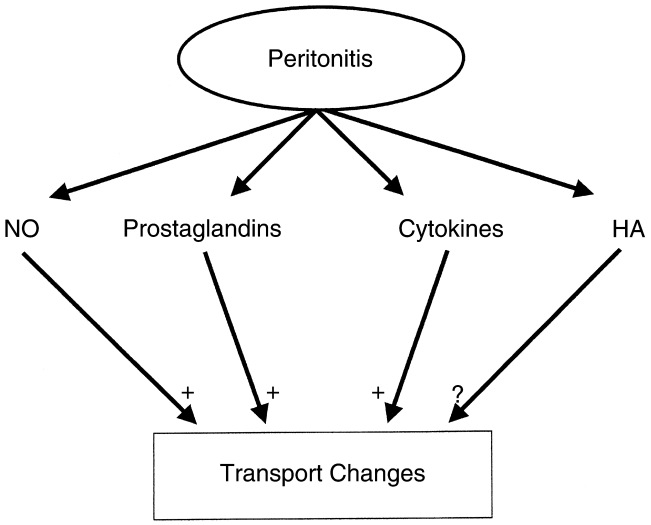

Fig. 8. Schematic of the interrelated effects of various mediators induced by peritonitis in inducing or modulating the transport changes observed during peritoneal inflammation.

Chronic effects of peritonitis

The effect of peritonitis on the long-term integrity of the peritoneal membrane in peritoneal dialysis (PD) has been the subject of intense investigation, but a uniform consistent picture has not emerged. This is mainly due to the variability of the clinical syndrome, the wide range of severity, and the paucity of sequential studies in affected patients.

Fussholler et al found that patients with a history of peritonitis were not different from patients without a previous peritonitis episode in terms of D/P ratio and mass transfer area coefficient of low molecular weight solutes, lymphatic absorption rate, transcapillary ultrafiltration, and net ultrafiltration [33]. Similarly, Wong et al observed that the longitudinal changes in peritoneal transport were independent of the history of peritonitis [34]. The findings are different, however, after severe peritonitis episodes. The prospective longitudinal study of Davies et al showed that clusters or recurrences of peritoneal infection caused a higher D/P creatinine and a lower ultrafiltration after recovery, than the previous values obtained in a stable situation [35]. A similar effect was found by Selgas et al [36]. Szeto et al examined the transport changes that developed in patients with severe peritonitis necessitating removal of Tenckhoff catheter [37]. Of 51 patients who had undergone a successful reinsertion of catheter and resumed PD, 11 patients were changed to long-term hemodialysis within eight months after their return to CAPD. After resuming peritoneal dialysis, a significant decline was found in net ultrafiltration volume and a trend toward a rise in D/P creatinine ($P = 0.15$). In a separate study, the same group investigated severe peritonitis defined as an episode that required catheter removal or antibiotic therapy for more than three weeks. After severe peritonitis, affected patients had higher increase in D/P creatinine over a period of two years than patients who experienced no severe infection [34].

Use of icodextrin

Icodextrin can be expected to induce the highest ultrafiltration rates in patients with a large effective or anatomical vascular surface area reflected in a high D/P creatinine. This is because the removal of icodextrin from the peritoneal cavity is predominantly via convective pathways (lymphatic absorption), while that of glucose is mainly by diffusion. A large vascular surface area allows high ultrafiltration rates, but this effect is counteracted by a rapid dissipation of the osmotic gradient with glucose-based solutions. In contrast the colloid osmotic pressure gradient remains present during the dwell when icodextrin is used. Increased ultrafiltration rates in patients with high D/P ratios or mass transfer area coefficients of creatinine have been described [38, 39]. This effect also could be induced after intraperitoneal administration of nitroprusside [40]. Based on these findings high ultrafiltration rates can be expected during peritonitis. This indeed had been the clinical experience as reported from various centers [abstracts; Dratwa et al, *Perit Dial Int* 18(Suppl 2):S74, 1998; Dratwa et al, *Perit Dial Int* 17(Suppl 1):S31, 1997; Posthuma et al, *J Am Soc Nephrol* 8:270A, 1997] [41–43]. The findings of these studies have been uniformly consistent: a decline in ultrafiltration during peritonitis with the use of glucose-based dialysis solutions and a stable or increased ultrafiltration response to icodextrin-based solutions.

In a randomized study on the efficacy of icodextrin versus glucose in thirty-eight patients on automated peritoneal dialysis (APD), Posthuma et al had the opportunity to prospectively compare the clinical efficacy of icodextrin during episodes of peritonitis (abstract; *ibid*) [42, 43]. Thirty peritonitis episodes occurred during follow-up. Daytime dwell UF decreased significantly during peritonitis glucose, but remained stable in icodextrin patients compared to non-peritonitis measurements (Fig. 9). Serum icodextrin metabolites remained stable during peritonitis; serum maltose concentrations did not change from steady state levels, nor did total icodextrin levels. These findings have been corroborated experimentally by Wang et al [11]. Therefore, it can be concluded that the use of icodextrin for the long dwells during peritonitis, both in CAPD and APD induces more net ultrafiltration than glucose-based solutions, thereby strengthening the results of the pathophysiological studies.

HIGH TRANSPORT AND UF FAILURE DURING CHRONIC PD

The transport abnormalities underlying ultrafiltration failure during chronic PD are not monolithic and the co-

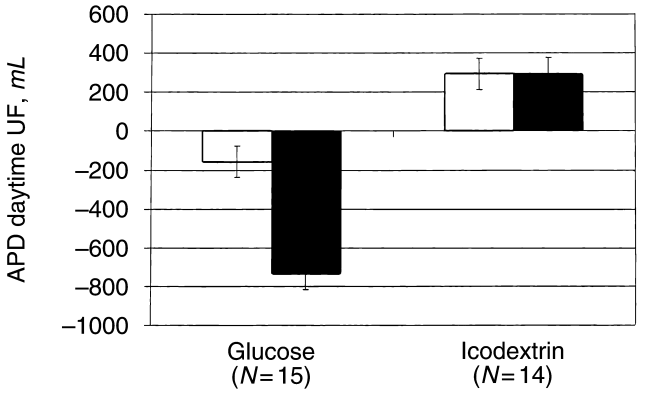

Fig. 9. Peritonitis in patients on automated peritoneal dialysis (APD) results in an accentuation of negative net ultrafiltration observed during the long daytime dwell with the use of glucose-based dialysis solutions. In patients using icodextrin for the daytime dwell, the positive net ultrafiltration is maintained despite the occurrence of peritonitis. Symbols are (□) non-peritonitis; (■) peritonitis. Data are from (abstract; Posthuma et al, *J Am Soc Nephrol* 8:270A, 1997) [42, 43].

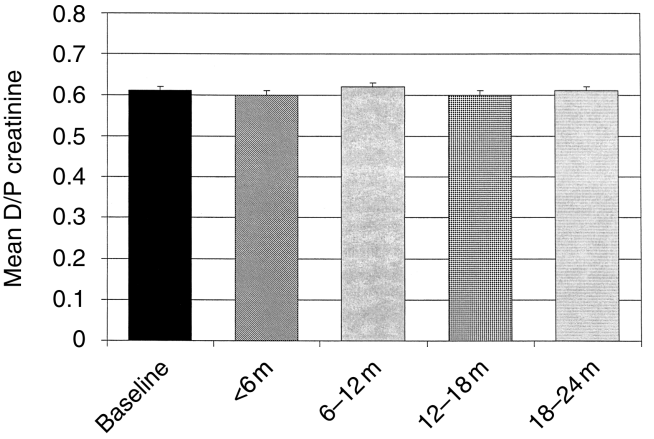

Fig. 10. Results of D/P creatinine at four hours obtained from repeat peritoneal equilibrium tests (PETs) during chronic PD. All patients had a minimum of 2 PETs during the follow-up, and many three to four evaluations.

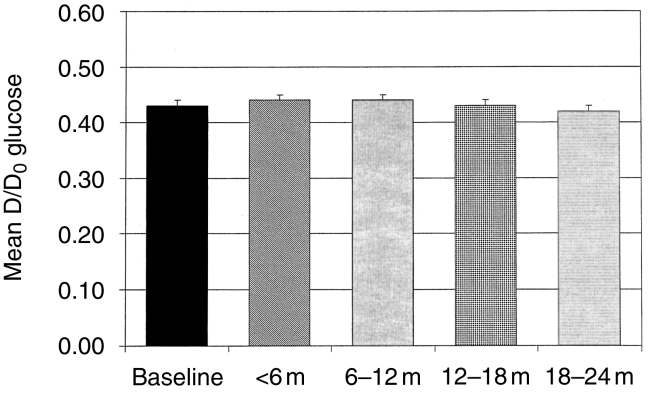

Fig. 11. Results of D/D_0 glucose at four hours obtained from repeat PETs during chronic PD. All patients had a minimum of two PETs during the follow-up, and many three to four evaluations.

existence of synergistic derangements is a possibility that has been recognized in the formulation of the clinical guideline on ultrafiltration failure [4, 7]. A fast transport status (high D/P ratio of low molecular weight solutes), however, either alone or in combination with other alterations in membrane function, remains the most common underlying mechanism [4, 7].

Temporal changes in membrane function

Peritoneal ultrafiltration capacity and small-solute transport characteristics are relatively stable in most patients treated with PD for three to five years [abstract; Hung, *Perit Dial Int* 22(Suppl):S10, 2002] [2, 34–36]. Wong et al have recently examined longitudinal changes in the peritoneal equilibration test in 64 patients [34]. No significant change in peritoneal solute transport was seen after two years. A centripetal pattern of the change in D/P creatinine was observed which probably reflects a regression-to-mean phenomenon. Similar results have been reported by Hung in 76 patients (abstract; *ibid*) and by one of us in a study of 230 paired peritoneal equilibrium tests (PETs) in CAPD patients from Turkey (Figs. 10 and 11) (unpublished observations).

While the overall pattern of peritoneal transport is stable, some patients treated with PD for four years or more develop increasing diffusive transport of low molecular weight solutes leading to a decreased net ultrafiltration on glucose-based solutions. This suggests an enlargement of the vascular peritoneal surface area. An increase in the number of peritoneal blood vessels with the duration of PD has been described [44]. Their density per unit length of peritoneum was significantly higher for patients with membrane failure [45], and implies the presence of a morphological substrate for the functional alterations. Based on a clinical definition Heimburger et al found that the prevalence of ultrafiltration failure increased from 3% during the first year of CAPD to 31% after six years of treatment [46]. Using a standardized dwell, this complication was found in 35% of patients treated with PD for more than four years (abstract; Smit et al, *Perit Dial Int* 22:117, 2002). Continuous exposure of the peritoneum to hypertonic glucose solutions may have a causative role in changes in peritoneal function. Davies et al have recently presented evidence suggesting that increased exposure to glucose precedes changes in solute transport in a selected group of long-term PD patients [47]. Of 22 patients who were treated continuously for five years, 13 had stable solute transport (D/P creatinine at start, 0.67; at 5 years, 0.67), whereas 9 had a sustained increase (D/P creatinine at start, 0.56; at 5 years, 0.77). Compared with the stable patients, those with increasing transport had earlier loss in residual renal

function and were exposed to significantly more hypertonic glucose during the first two years of treatment that preceded the increase in solute transport [47]. Further increases in glucose exposure were observed as solute transport continued to rise. In this selected group of long-term survivors on PD, an increase in solute transport with time was preceded by increased peritoneal exposure to hypertonic glucose. Besides many other observations, this is supportive evidence that hypertonic glucose may play a causative role in alterations in peritoneal membrane function.

A high lymphatic absorption rate can contribute to ultrafiltration failure [33, 46], and this is illustrated in the recent report by Smit et al (abstract; *ibid*) [51]. In a cross sectional study of 20 long-term PD patients with UF failure, a mixed defect (an increase in small solute diffusive transport with a simultaneous increase in lymphatic absorption) was observed in 12 patients and unique abnormalities were observed in only 6. These findings indicate that increased small solute diffusive transport remains the most commonly observed transport alteration and that synergistic changes in lymphatic absorption may occur more commonly than previously assumed. It must be emphasized that these measurements were done using the disappearance rate of intraperitoneally administered macromolecular tracers, which are taken up into the lymphatics that drain the peritoneal cavity, but also in peritoneal interstitial tissue. It is unknown whether lymphatic absorption from the peritoneal cavity increases with the duration of peritoneal dialysis.

Use of icodextrin

Because of its large molecular weight, icodextrin exhibits a kinetic profile that makes it uniquely suited for use as an alternative to glucose in patients with increased small solute diffusive transport. This has been discussed in the section on peritonitis and has recently been confirmed by other groups, both in observational studies [48] and in a randomized double-blind controlled trial (Fig. 12) (abstract; Wolfson et al, *J Am Soc Nephrol* 12: 317A, 2001). The increase in ultrafiltration volume was associated with an increase in convective transport of low molecular weight proteins such as β_2-microglobulin (abstract; Opatrna et al, *J Am Soc Nephrol* 12:314A, 2001) [48, 49] and leptin (abstract; Opatrna, *ibid*) [56]. Similar results on the relationship between peritoneal transport status and icodextrin-induced ultrafiltration have recently been reported by Pecoits-Filho et al [abstract; *Perit Dial Int* 22(Suppl):S13, 2002], who additionally suggested a correlation between high transport status and effluent IL-6 and VEGF. A relationship between dialysate VEGF and peritoneal transport also was found by Van Esch et al in patients during their first half year of PD [abstract; *Perit Dial Int* 22(Suppl):S16, 2002].

The role of icodextrin in the clinical management of

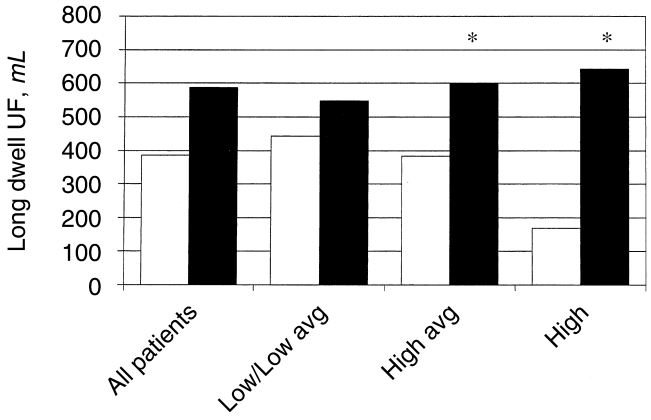

Fig. 12. Net ultrafiltration response to (■) icodextrin and (□) 2.5% dextrose by PET transport type. Redrawn from data in (abstract; Wolfson et al, *J Am Soc Nephrol* 12:317A, 2001).

patients with ultrafiltration failure was recognized early after the introduction of icodextrin-based peritoneal dialysis solutions. Stein et al described the course of 61 patients with ultrafiltration failure treated with icodextrin. The majority of patients could be maintained on PD after the addition of icodextrin and only eight patients were subsequently transferred to HD because of recurrent ultrafiltration failure after a minimum of eight months on icodextrin [50].

Wilkie et al provided a long-term follow-up of response to icodextrin in 33 patients with clinical ultrafiltration failure as defined above. CAPD technique survival was extended by a median of 22 months in patients who would have otherwise required transfer to hemodialysis [51]. Johnson et al recently examined the use of icodextrin as salvage therapy for refractory fluid overload in a prospective, open-label study of 17 patients on peritoneal dialysis [52].

Icodextrin was substituted for 4.25% dextrose for the long dwell exchange in patients were on the verge on being transferred to hemodialysis because of symptomatic fluid retention that was unresponsive to fluid restriction, loop diuretic therapy, hypertonic dextrose exchanges, and dwell time optimization. Icodextrin increased daily peritoneal ultrafiltration (UF) by 599 mL (885 $\pm$ 210 mL to 1454 $\pm$ 215 mL, $P < 0.05$) and reduced mean arterial pressure by 10 mm Hg (106 $\pm$ 4 mm Hg to 96 $\pm$ 4 mm Hg, $P < 0.05$) [52]. Overall PD technique survival was prolonged by a mean of 11.6 months (95% CI 6.0 to 17.3 months). Diabetic patients experienced improvement in glycemic control as evidenced by a decrease in hemoglobin A1c from 8.9 $\pm$ 0.7% to 7.9 $\pm$ 0.7%. Seven of the 12 patients required a reduction in insulin dose [52].

In summary, a state of increased diffusive transport of small solutes appears to be operative in most cases of clinical ultrafiltration failure. In patients with acute peritonitis, the increase in small solute diffusive transport

appears to be the predominant and only mechanism underlying the decline in ultrafiltration capacity. In patients who develop ultrafiltration failure during long term PD, high diffusive transport of small solutes remains the most commonly observed underlying cause. In a number of cases, however, a synergistic ancillary mechanism (such as lymphatic absorption) appears to be operative as well. Icodextrin has been found to be clinically effective in restituting UF in both patients with peritonitis and patients with ultrafiltration failure during chronic PD. This clinical success of icodextrin is due to its unique mechanism of action as a colloid osmotic agent.

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